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Early versus delayed treatment with ticagrelor on residual thrombus after percutaneous coronary intervention in patients presenting with non-ST-elevation acute coronary syndrome: an optical coherence tomography study

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Ticagrelor, a P2Y12 antagonist, is well known for its rapid, high-potent inhibition of platelet aggregation by pharmacokinetic studies [1]. In the PLATO study, ticagrelor, compared to clopidogrel, reduced the incidence of myocardial infarction, stroke, cardiovascular death and definite stent thrombosis, during 12-month follow-up in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) [2,3]. To date, the effect of early ticagrelor administration versus treatment at the time of PCI has not been well studied. The ATLANTIC study demonstrated that prehospital administration of ticagrelor did not improve pre-PCI coronary reperfusion compared to in-hospital treatment [4].

We aimed to compare the effectiveness of antiplatelet therapy by measuring the differences in residual thrombus burden after PCI by optical coherence tomography (OCT) between immediate and delayed initiation of ticagrelor in patients with ACS.

This was a prospective, randomized study involving eight Korean centers. Patients presented with non-ST-elevation ACS (NSTE-ACS) were screened between July 2016 and November 2017. All patients who were scheduled to undergo coronary angiography between 4 and 72 h after randomization were eligible. Patients with NYHA class III or IV heart failure or known left ventricular ejection fraction <30% and hemodynamic or electrical instability were excluded. Patients were randomized 1:1 to receive 180 mg of ticagrelor either immediately after a diagnosis of NSTE-ACS was made (early treatment group) or after diagnostic coronary angiography but prior to PCI (delayed treatment group). Patients randomized to the early treatment group received a maintenance dose of 90 mg every 12 h until the time of catheterization. Both the early treatment group and the delayed treatment group have received aspirin loading dose of 300 mg after the diagnosis of NSTE-ACS, and maintained 100 mg a day until angiography was done. After PCI, patients were maintained on ticagrelor and aspirin. Patients were followed through their index hospitalization. The study was approved by the institutional ethics committee at each participating hospital and informed consent was obtained prior to the enrollment.

The primary end point of this study was residual thrombus burden assessed by post-PCI OCT. A frequency-domain OCT system was used. Statistical analyses were performed using SPSS v. 12.5 for Windows and $P < 0.05$ was considered to indicate a statistically significant difference.

A total of 100 patients enrolled in the study were randomly assigned to either early treatment group (n = 50) or delayed treatment group (n = 50) (Fig. 1). There was no significant difference in baseline patient characteristics between the groups (Table 1). The degree of platelet inhibition was significantly higher in the early treatment group than in the delayed treatment group [P2Y12 reaction units (PRU), 70.6 ± 62.1 versus 227.2 ± 76.6; $P < 0.001$]. The median interval between the administration of ticagrelor and PCI in the early treatment group was 854 min. The primary end points of this study, thrombus area, length, volume and thrombus burden were not different between two groups (Table 1). No stent thrombosis or major bleeding occurred.

To our knowledge, this is the first study that prospectively compared the effects of early versus delayed administration of ticagrelor on residual thrombus burden after PCI with OCT in patients with NSTE-ACS. We hypothesized that early administration of ticagrelor would lead to more profound suppression of platelet reactivity at the time of PCI, and therefore, would lead to smaller residual thrombus burden. Indeed, our results showed that the early treatment group had lower values of PRU at the time of PCI; nevertheless, no significant difference in residual thrombus burden was found between the two groups. Possible explanations include the following: (1) the time difference of 14 h was not long enough to see the difference in thrombus burden. However, in real world practice, the usual time delay between presentation to

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Fig. 1

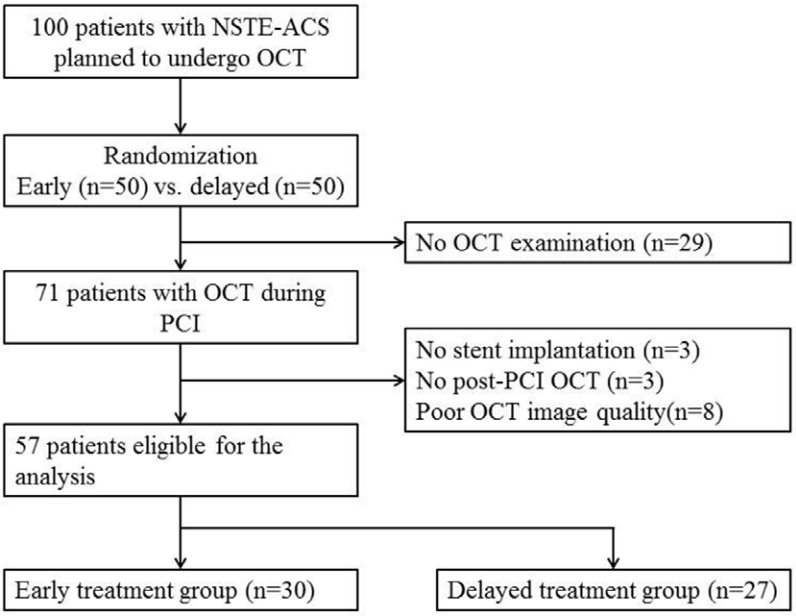

Diagram of the study design. NSTE-ACS, non-ST-elevation acute coronary syndrome; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Table 1 Baseline, angiographic and optical coherence tomography characteristics

	Early treatment, N = 30	Delayed treatment, N = 27	*P* value
Baseline characteristics			
Male, n (%)	20 (66.6%)	20 (74.0%)	0.542
Age, years	63.8 ± 10.3	65.3 ± 10.3	0.596
Hypertension, n (%)	13 (43.3%)	13 (48.1%)	0.536
Diabetes mellitus, n (%)	6 (20.0%)	7 (25.9%)	0.594
Dyslipidemia, n (%)	9 (30.0%)	8 (29.6%)	0.976
LVEF, %	58.6 ± 10.9	58.4 ± 7.4	0.944
CK-MB, initial, μg/L	19.3 ± 37.2	10.0 ± 12.7	0.222
CK-MB, peak, μg/L	48.6 ± 67.0	57.6 ± 89.0	0.672
Troponin-I, initial, μg/L	7.3 ± 27.4	2.2 ± 5.1	0.347
Troponin-I, peak, μg/L	15.7 ± 33.8	5.7 ± 9.2	0.159
PRU	70.6 ± 62.1	227.2 ± 76.6	<0.001
Interval between administration of ticagrelor and procedure, min	854.0 ± 671.0	0	<0.001
Angiographic characteristics			
Culprit lesion, n (%)			0.368
Left anterior descending	17 (56.6%)	15 (55.5%)	
Left circumflex	5 (16.6%)	8 (29.6%)	
Right coronary artery	8 (26.6%)	4 (14.8%)	
Stent length, mm	25.5 ± 8.2	24.1 ± 8.3	0.607
Stent volume, mm^3	156.5 ± 57.9	161.7 ± 63.9	0.524
Maximal thrombus area, mm^2	0.57 ± 0.21	0.45 ± 0.26	0.075
Mean thrombus area, mm^2	0.21 ± 0.07	0.18 ± 0.09	0.165
Thrombus length, mm	11.30 ± 5.57	9.11 ± 4.47	0.110
Thrombus volume, mm^3	2.38 ± 1.48	1.87 ± 1.42	0.189
Thrombus burden, %	1.64 ± 1.10	1.24 ± 0.92	0.143
Pre-TIMI flow 0-1, n (%)	8 (26.6%)	3 (11.1%)	0.186
Post-TIMI flow 3, n (%)	29 (96.6%)	27 (100%)	1.000

CK-MB, creatine kinase myocardial band; LVEF, left ventricular ejection fraction; PRU, P2Y12 reaction units, TIMI, thrombolysis in myocardial infarction.

a hospital and catheterization in patients with NSTE-ACS is 22 h [5]. (2) Although ticagrelor is a potent P2Y12 inhibitor, it may not be potent enough to show difference in thrombus burden. (3) The number of patients was small. Moreover, a significant number of patients did not undergo post-PCI OCT imaging.

The earliest administration of ticagrelor may be preferable to achieve early efficacy, but in cases in which NSTE-ACS is not clearly diagnosed, it should be considered to delay the loading of P2Y12 inhibitor until the angiographic lesion is observed. Prospective larger scale randomized controlled trials are needed to investigate the clinical outcomes such as myocardial infarction, cardiac death, stroke and major bleeding events.

To conclude, early administration of ticagrelor at the time of presentation showed a greater level of platelet inhibition, but did not show benefit in reduction of thrombus burden following PCI in patients presenting with NSTE-ACS.

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Conflicts of interest

There are no conflicts of interest.

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Necessity of back-up pace maker support during acetylcholine testing as a safe method

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Introduction

Intracoronary acetylcholine (ACh) testing was first reported by Yasue and Okumura in 1986 [1]. According to the Japanese Circulation Society (JCS) guidelines, temporary pacing is necessary when performing intracoronary ACh spasm provocation tests [2]. Ong *et al.* reported the ACh testing for over 3 min administration without pace maker (PM) [3]. In this article, we examined the incidence of back-up PM supports during intracoronary ACh spasm provocation test based on the JCS guidelines.

Methods

From October 2012 to November 2017, we tried to perform ACh spasm provocation tests in 315 patients (male: 242 patients, mean age of 67.5 ± 10.9 year) whenever possible. As show in Table 1, ischemic heart disease (IHD) was observed in 237 patients, whereas non-IHD was found in 78 patients. We classified these 315 patients into two groups consisting of with and without back-up PM support during ACh testing. We defined positive provoked spasm as ≥90% transient narrowing and usual chest pain or ischemic ECG changes.

All drugs except for nitroglycerine were discontinued for ≥24 h before the study. A temporary PM was inserted into the right ventricle of each patient and the pacing rate was set at 40 beats/min. We defined positive back-up PM support as any pacing during ACh testing. ACh chloride was injected in incremental doses of 20, 50 and 80 μg into the right coronary artery (RCA) and of 20, 50, 100 and 200 μg into the left coronary artery (LCA) over 20 s with at least a 3-min interval between each injection [4,5]. The study protocol complied with the Declaration of Helsinki. Written informed consent about performing the ACh spasm provocation tests was obtained from all patients and the protocol of this study was in agreement with the guidelines of the ethical committee at our institution.

Statistical analysis

Data analysis was carried out with SPSS (version 22.0, IBM Japan, Ltd., Tokyo, Japan). All data were presented as the mean ± 1 SD and analyzed by the Fisher's exact test with correction or the Mann–Whitney test. $P < 0.05$ was considered significant.

Results

We used the 5 French temporary PM. Brachial vein approach was employed n 252 patients (80%), while femoral vein was used in the remaining 63 patients (20%). As

Table 1 Clinical characteristics in all patients

	Total	With back-up PM	Without back-up PM
Number	315	293	22
Male (%)	242 (76.8%)	224 (76.5%)	18 (85.0%)
Age (year)	67.5 ± 10.9	68.0 ± 10.8	61.7 ± 10.8*
Organic stenosis	41 (13.0%)	39 (13.3%)	2 (9.1%)
History of smoking	226 (71.7%)	211 (72.0%)	15 (68.2%)
Hypertension	185 (58.7%)	173 (59.0%)	12 (54.5%)
Dyslipidemia	196 (62.2%)	183 (62.5%)	13 (59.1%)
Diabetes mellitus	107 (34.0%)	97 (33.1%)	10 (45.4%)
Ischemic heart disease	237 (75.2%)	224 (76.5%)	13 (59.1%)
Rest	83 (26.3%)	78 (26.6%)	5 (22.7%)
Effort	29 (9.2%)	27 (9.2%)	2 (9.1%)
Rest and effort	23 (7.3%)	22 (7.5%)	1 (4.5%)
Healed myocardial infarction	9 (2.9%)	9 (3.1%)	0
Postpercutaneous coronary intervention	93 (29.5%)	88 (30.0%)	5 (22.7%)
Nonischemic heart disease	78 (24.8%)	69 (23.5%)	9 (40.9%)
Atypical chest pain	22 (7.0%)	19 (6.5%)	3 (13.6%)
Dilated cardiomyopathy/ congestive heart failure	18 (5.7%)	13 (4.4%)	5 (22.7%)**
Hypertrophic cardiomyopathy	3 (1.0%)	3 (1.0%)	0
Valvular heart disease	2 (0.6%)	2 (0.7%)	0
Syncope	13 (4.1%)	13 (4.4%)	0
Other	20 (6.3%)	19 (6.5%)	1 (4.5%)
Provoked spasm	206 (65.4%)	195 (66.6%)	11 (50.0%)
In the right coronary artery	148 (47.0%)	141 (48.1%)	7 (31.8%)
In the circumflex artery	84 (26.7%)	79 (27.0%)	5 (22.7%)
In the left anterior descending artery	162 (51.4%)	152 (51.9%)	10 (45.4%)
Single vessel spasm	76 (24.1%)	71 (24.2%)	5 (22.7%)
Double vessel spasm	72 (22.9%)	71 (24.2%)	1 (4.5%)
Triple vessel spasm	58 (18.4%)	53 (18.1%)	5 (22.7%)

PM, pace maker.
*$P < 0.05$ and **$P < 0.001$ vs. with back-up PM.